

## **Pelvic Ultrasound for Diagnosis of Precocious Puberty**

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Precocious puberty (PP) in girls is defined as the appearance of secondary sex characteristics before the age of 8 years. In most cases, it is caused by premature activation of the hypothalamic gonadotropin releasing hormone (GnRH) pulse generator ("central" PP) and is considered to be idiopathic. Central PP (CPP) may cause early epiphyseal maturation with compromised final height (1) as well as psychological stress (2,3). Thus, early initiation of treatment is important (4).

Like CPP, premature thelarche (PT) is characterized by early breast development, but it is not associated with acceleration of growth or bone maturation and thus does not require therapy (5).

The incidence of PT is highest in the first year of life, falls in the second, third and fourth years, and then slightly increases after the fifth year (6). In some cases, the latter increase may represent an "intermediate" entity between isolated PT and CPP (7), also called "thelarche variant", "non-classical PT" and "atypical PT". Girls with thelarche variant have an older age at onset and occasional progression to CPP (8).

With the significant increase in obesity prevalence in recent years, the distinction between CPP and obesity with or without thelarche poses another diagnostic challenge. Bone age may be advanced in obese girls who present with pseudobreast due to increased fat tissue (9,10), whereas bone age advancement and growth acceleration might not be observed in the early stages of CPP.

Clinically, the diagnosis of CPP is based on physical examination, bone age assessment, and growth.

The GnRH stimulation test is the current gold standard for diagnosis because of its high accuracy.

However, validation studies have reported a low sensitivity (11-13), and researchers disagree on the diagnostic cut-off response to the test. Pelvic ultrasound scan is also used as a diagnostic tool in PP to rule out functional ovarian cysts or tumor as a cause of the symptoms. In addition, since the quality

of the ultrasound scan is not affected by obesity, it may serve as a helpful, accurate adjunct when PP needs to be differentiated from PT or obesity.

### **How is pelvic ultrasound performed?**

Pelvic ultrasound scans are performed by the transabdominal approach using a conventional, full-bladder, 5-MHz, real-time sector scanner. The uterus and ovaries are visualized in both transverse and longitudinal sections. The following parameters are measured:

1. Uterus: Length, transverse diameter (width), endometrial thickness, fundal anteroposterior diameter, and cervical anteroposterior diameter. The ratio between the fundal and cervical diameters (FCR) is calculated. Uterine length is multiplied by the fundal anteroposterior diameter to determine the uterine cross-sectional area.
2. Ovaries: Height, width, length, number of follicles, and maximal diameter of largest follicle observed. Ovarian circumference can be measured in the transverse position.

Uterine and ovarian volumes are calculated according to the formula for ellipsoid bodies:  $V = \text{longitudinal diameter} \times \text{anteroposterior diameter} \times \text{transverse diameter} \times 0.5233$ .

### **Normal pelvic ultrasound in girls**

The size and morphology of the uterus and ovaries remain relatively stable from infancy to before puberty. At infancy, the uterine fundus and cervix, owing to their similar width, form a tubular configuration (14), so that the FCR is approximately 1. Starting at around age 9 years, they undergo progressive increases in size which are strongly correlated with the pubertal stages (15). The uterine body also becomes wider than the cervix and takes on the typical adult pear shape (15-19). An endometrial echo is found in 97% of infants aged less than 1 week (20), and in 50% of girls aged less than 6 months. In older prepubertal subjects, there is no endometrial echo before stage B2 of puberty. The presence of ovarian follicles (microcysts) at any age is physiologic, merely indicating anovulation and follicle-stimulating hormone activation. The follicular diameter in prepubertal girls usually ranges from 2.0 to 9.0 mm. However, the occasional presence of large follicles (up to 12 mm) in this age

group, owing to lower levels of gonadotropin secretion, limits the usefulness of follicular diameter measurement in the assessment of pubertal status (21).

### **Pelvic ultrasound in precocious puberty and in premature thelarche**

Significant differences in pelvic ultrasound parameters have been reported between healthy girls and age-matched girls with CPP (16,22) but not with PT, and between girls with CPP and age-matched girls with PT. Uterine transverse diameter ("width"), uterine length, fundal anteroposterior diameter, uterine volume, ovarian length, ovarian circumference, and mean ovarian volume are all increased in girls with CPP. The presence of endometrial echo in CPP is very specific, but of low sensitivity.

The calculated cut-off values to predict PP by ultrasound vary among studies. Haber et al (11) found that a uterine volume >1.8 ml, uterine length >3.6 cm, and ovarian volume >1.2 ml were highly predictive for PP. Herter et al (23) reported that the best cut-off points were uterine length 4.0 cm, uterine cross-sectional area  $4.5 \text{ cm}^2$ , uterine volume  $3.0 \text{ cm}^3$ , and ovarian volume  $1.0 \text{ cm}^3$ . In a previous study by our group, predictive cut-off levels were as follows: uterine anteroposterior diameter >8 mm, uterine transverse diameter >1.5 cm; uterine length >3.4 cm, uterine volume >1.96 ml, and ovarian circumference >4.5 cm. The sensitivity and specificity of most of the significant variables are shown in Table 1. The low sensitivity of the sonographic findings, shown in most studies, is attributable to the large overlap of normal and pathological values in the prepubertal age (22,24).

Figure 1 presents continuous data for some of the crucial measures, marking individual points as PT versus CPP. Nevertheless, pelvic ultrasound has proved to be an efficient tool in the distinction between CPP and PT, especially when the results of the GnRH stimulation test are equivocal (22,23). Overall, uterine parameters contribute more than ovarian parameters to the differentiation of these disorders.

Uterine artery Doppler analysis may also assist clinicians in the diagnosis of PP. Battaglia et al (24) found that the presence of a low pulsatility index (<2.5) at the level of the uterine arteries had a high diagnostic value for PP. However, there are only few studies so far of the diagnostic role of Doppler

ultrasound in PP, and further longitudinal investigations are necessary.

Pelvic ultrasound has additional advantages in paediatric endocrinology. Because the data from the ultrasound scan are obtained at the same time as the physical examination, its use provides the clinician with a broader clinical view and saves the patient and the institute time and money. The test is also not very stressful for the girls, as the surroundings are already familiar to them. Unfortunately there is no one parameter that is accurate and sensitive enough to distinguish among the different presentations of premature sexual development.

### **Summary**

Above-normal uterine and ovarian measurements on pelvic ultrasound serve as an early and sensitive sign of CPP. These changes may appear before changes in the GnRH test can be detected. Thus, pelvic ultrasound, a noninvasive, inexpensive, and reliable tool, may provide the clinician with a complementary indication to the GnRH test for the distinction between isolated PT and early-stage CPP in girls with early breast budding. Therefore, we believe it should be included in the routine work-up of girls with suspected PP.

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**Table 1. Sensitivity, Specificity , Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of Most Significant Clinical Parameters on ANOVA**

	<b>Sensitivity</b>	<b>Specificity</b>	<b>PPV</b>	<b>NPV (%)</b>
	<b>(%)</b>	<b>(%)</b>	<b>(%)</b>	
Uterine transverse diameter > 1.5cm	67.9	100	100	39.5
Presence of endometrial echo	57.3	100	100	40.7
Fundus >0.8 cm	82.5	76.4	94.2	48.1
Uterine length >3.4 cm	80.2	57.8	89	40.7
Uterine volume >2.0 ml	88.8	89.4	97.2	65
Ovarian circumference >4.5 cm	66.6	85.7	95.4	36.3
Androstendione >1.0 nmol/L	59	76	89	35.5
Peak LH >5 mIU/ml	58	93.7	98	33.3
Bone-age SDS >1	73.3	81.8	93.2	47.3

LH = luteinizing hormone

SDS = standard deviation score

Figure 1 Individual clinical and ultrasound data of girls with central precocious puberty (CPP) or premature thelarche (PT).

Note: The horizontal lines indicate the median for each group.